# Environmental Factors in the Etiology of Rhabdomyosarcoma in Childhood [1, 2, 3]

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ABSTRACT—In a case-control study of childhood rhabdomyosarcoma (RMS), families of 33 cases and 99 controls were interviewed. A relative risk (RR) of 3.9 was found associated with fathers' (but not mothers') cigarette smoking ($P=0.003$). Cases had had fewer immunizations than controls, particularly smallpox vaccination (RR=0.2; $P=0.001$), and conversely had more preventable infections. An RR of 3.2 ($P=0.03$) was found associated with exposure to chemicals and an RR of 3.7 ($P=0.004$) was found associated with diets that included organ meats. Mothers of cases were more likely to be over age 30 years at subject's birth, to have used antibiotics preceding or during pregnancy, and to have had an overdue and/or assisted delivery. Other findings suggest that low socioeconomic status is associated with an increased risk of RMS. These aggregate findings imply that environmental factors may play an important role in the etiology of childhood RMS.—JNCI 1982; 68:107-113.

RMS is the sixth most common cancer of childhood with an annual incidence of about 4 cases per million children (*1, 2*). Little is known about its epidemiologic features, and there are few etiologic hypotheses for this rare disease. Previous epidemiologic studies, based on mortality statistics and case series, indicate the following: Males are more susceptible than females, with whites being more susceptible than blacks; the peak incidence is at about ages 3-4 years; relatives of patients are at markedly increased risk of RMS; and there appears to be familial aggregation of RMS with other soft tissue sarcomas and breast cancer (*3-5*). In this first case-control study of childhood RMS we evaluated possible etiologic factors.

## SUBJECTS AND METHODS

We attempted to identify all incident cases of childhood RMS in NC residents during the period 1967-76. Diagnostic indexes, tumor registries, and pathology logs were searched at 141 of the 150 nonpsychiatric hospitals in NC that admit children and at three major referral hospitals in two adjacent states. The nine nonparticipating institutions were military hospitals, which usually referred their pediatric oncology patients to in-state civilian hospitals for care. A total of 37 cases was identified, and the subjects were 0-14 years of age; all but 1 were diagnosed at an NC hospital. We also searched the NC State Tumor Registry and oncology records at the (then) three NC medical schools but found no additional cases. To be eligible for study, a patient ("case") had to have been born in NC and reside there at the time of a histopathologically confirmed diagnosis. Because birth certificates served as our means of selecting controls, cases also had to have a birth certificate on file with the NC Department of Human Resources. Four of the 37 cases were excluded: Two had been born out of state; 1 had been adopted (hence her birth certificate was not publicly listed), and another, although born in NC, had no birth certificate on file. For each of the 33 resulting cases, 3 controls of the same age (±2 mo), sex, and race were randomly selected from NC birth certificates. We excluded subjects who had been adopted, who had died during the neonatal period, or who had been born to parents serving in the military.

Recent addresses for case families were obtained in most instances from their physicians and from medical records. Current addresses for the parents of controls were obtained by a variety of means. The first resource was a library of telephone and city directories from which we tried to match an address with that on the birth certificate. Where necessary, we next searched driver's license and motor vehicle registries. In some instances it was possible to trace parents through the physician listed on the birth certificate. Our last resort was to visit the town of last known address and make inquiries of neighbors and at the post office.

Abbreviations used: NC=North Carolina; RMS=rhabdomyosarcoma; RR=relative risk(s); SES=socioeconomic status.

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We were thus able to trace all 33 cases. Of the 99 controls first selected, only 70 were found and interviewed; 9 were located but refused to participate, and the other 20 were untraceable. These 29 controls were then replaced by children whose birth certificates were selected by the same methods described above. Twenty-three of these replacements were located and interviewed; 1 more was located but refused to participate, and the other 5 could not be found. A second replacement was chosen for these 6 controls by the same methods. Five of the 6 second-round replacements were interviewed, and 1 refused to cooperate. This control was replaced by a third-round selection.

Using the information on birth certificates, we assessed bias potentially introduced by our loss and replacement of original controls. First, we compared the participating original (first-round) controls with all of the lost and nonparticipating ones and found similar distributions of sex, race, date of birth, extent of parents' education, parents' age at birth of subject, region of residence, duration of pregnancy, and father's occupation (table 1). This finding indicates that the lost and nonparticipating controls were quite similar to the participating first-round controls. Second, we compared the lost and nonparticipating controls with their replacements. As shown in table 1, the only major difference between these 2 groups was in the area of father's occupation. Fewer replacement controls had fathers with professional or managerial occupations, and replacements had more prenatal visits.

Since our evaluation of potential bias was based on birth certificate information, we assessed the reliability of this information by checking it against our interview data. The correlation between fathers' occupations (in terms of "professional and managerial" vs. "other") from the two sources was 0.83. Similarly, the correlation coefficient for years of fathers' education was 0.58 and for years of mothers' education, 0.68.

After case and control families had been located, they were invited by letter to participate in a "study of child health." Interviews were then arranged by telephone call or home visit if the family had no telephone. A standard questionnaire was administered by trained interviewers. The mean duration of interviews for cases was 70.5 minutes and that for controls, 65.1 minutes. All but eight interviews were conducted in the subjects' homes. Three took place at the mothers' place of employment (1 case and 2 control mothers) and one at Duke University Medical Center (a case); four were done by telephone because the families had moved out of NC (2 cases and 2 controls). The informant in all but two instances was the subject's parent, usually the mother (91% of cases and 92% of controls).

In our analyses, we estimated RR and 95% confidence intervals by using both matched and unmatched methods (*6–8*). Since results from both analyses were similar (the differences being <10%), only the unmatched results are presented. Since the purpose of our study was to generate hypotheses for later confirmation, we made no effort to adjust for the multiple testing situation in which we examined numerous potential risk factors. Even if none of the factors examined were related to risk of RMS, an analysis such as this would be expected to generate *P*-values of less than 0.05 for 5 of every 100 variables. Thus for those variables that we have found to be significant, the actual significance level may be greater than our stated *P*-value.

## RESULTS

*SES.*—The first group of variables examined were correlates of SES (table 2). We found the estimated RR associated with mothers' education beyond high school to be 0.3 ($P=0.04$); that for fathers was 0.5 ($P=0.13$). Similarly, the RR associated with mothers' having professional or managerial occupations was 0.4 and that for fathers was 0.5. The RR associated with annual family income of $10,000 or more was 0.5 ($P=0.09$). Whereas only one of these variables reached statistical significance at the 0.05 level, all RR were markedly low and deviated in the same direction from unity. This confluence of findings suggests that low SES is a risk marker for RMS.

*Family medical history.*—A second group of ques-

TABLE 1.—*Comparison of birth certificate information: Participating, lost and nonparticipating, and replacement controls*

| Birth certificate information | Participating original controls[a] | Lost and non-participating controls[b] | Replacement controls[c] |
|---|---|---|---|
| Percentage of fathers with professional or managerial occupations | 28 | 27 | 11 |
| Mean years of fathers' education | 11.6 | 10.5 | 12.0 |
| Mean years of mothers' education | 11.5 | 11.7 | 11.2 |
| Mean age of fathers at subjects' birth | 26.6 | 28.1 | 28.2 |
| Mean age of mothers at subjects' birth | 24.1 | 25.0 | 25.4 |
| Percentage of married mothers | 100 | 100 | 100 |
| Percentage of mothers attended by physician at delivery | 96 | 96 | 100 |
| Mean gestational period, wk | 38.5 | 38.4 | 39.1 |
| Mean No. of prenatal visits | 10.1 | 8.7 | 10.3 |

[a] No. = 70.
[b] No. = 36.
[c] No. = 29.

TABLE 2.—*Childhood RMS risk factors: Socioeconomic indicators*

| Risk factors | No. of cases (%) | No. of controls (%) | RR | 95% confidence interval |
|---|---|---|---|---|
| Mothers with ≥13 yr of education | 4 (13) | 31 (32) | 0.3 | 0.1–0.9 |
| Fathers with ≥13 yr of education | 6 (19) | 31 (33) | 0.5 | 0.2–1.3 |
| Mothers with professional or managerial occupations | 3 (14) | 18 (29) | 0.4 | 0.1–1.6 |
| Fathers with professional or managerial occupations | 6 (21) | 29 (34) | 0.5 | 0.2–1.5 |
| No. of families with annual income of $10,000 or more | 14 (44) | 59 (61) | 0.5 | 0.2–1.1 |

tions dealt with family history of disease (table 3). The estimated RR for cancer in relatives of cases versus controls was 2.3 ($P=0.08$). However, when restricted to first-degree relatives—where recall would be more complete for both cases and controls—there was little difference in history of cancer between case and control families (RR = 0.7). Thus there was probably "selective recall" bias wherein case families are more apt to remember cancer in remote relatives.

We found an association of RMS with family history of asthma or allergies (RR = 2.5; $P=0.03$). When we restricted this analysis to first-degree relatives only, we found little change. Thus this finding is probably not subject to selective recall. Despite the more frequent history of asthma and allergies in case families, the RR for relatives' having received "allergy shots" was 0.4; however, this finding was not close to being statistically significant. Perhaps related to the asthma and allergies finding was our finding of an RR of 1.9 associated with a family history of frequent or serious infections. We also found an association with family history of anemia (RR = 2.1).

*Gestational and delivery factors.*—Several gestational and perinatal factors appeared to be associated with RMS (table 4). Mothers' use of antibiotics within 1 year preceding or during the subjects' gestation conferred an RR of 2.7 ($P=0.03$). Additionally, the RR associated with mothers' being over 30 years of age at the time of delivery was 2.6 ($P=0.06$). The RR associated with overdue versus normal delivery was 2.8 ($P=0.03$); that associated with premature delivery was 0.6. Forceps or cesarean section delivery conferred an RR of 2.4 ($P=0.10$). Thus the age of the mother, the length of her pregnancy, "assisted delivery," and gestational use of antibiotics may be risk markers for RMS. The RR for radiographic examination during pregnancy in case mothers versus control mothers was 0.5.

*Neonatal history.*—The RR associated with a history of neonatal jaundice was 0.3; that associated with neonatal conditions requiring medical treatment was 0.4 (table 5). However, the occurrence of neonatal problems was infrequent in cases and controls and none of the associations in this category was statistically significant at the 0.05 level.

*Environmental exposures.*—We also examined several environmental exposures (table 6). We found an RR of 3.2 associated with exposure to chemicals other than pesticides and rodenticides. This category includes exposures to such substances as solvents, paints, acids, bleaches, fertilizers, and gasoline. The only substances to which more than 1 case was exposed were chemical fertilizers. Three cases (9%) and 1 control (1%) had been exposed to fertilizers, yielding an RR of 10.0 (1.5–68, 95% confidence interval). Some of the cases had more than one type of chemical exposure. Similarly, living near a factory that emitted chemical pollution conferred an RR of 3.3 ($P=0.24$).

*Diet.*—The estimate of RR associated with the eating of organ meats (e.g., liver, brain, and tongue) was 3.7 ($P=0.004$) (table 7). Case families also used less animal fat (lard) in cooking than did control families (RR = 0.4). No other dietary factors appeared remarkably associated.

*Immunization history.*—Cases had received far fewer routine childhood immunizations than had controls (table 8). The RR for smallpox vaccination was 0.2 ($P=0.001$), for measles-mumps-rubella immunization 0.3, and for diphtheria-pertussis-tetanus immunization 0.7. We assessed the RR associated with overall immunization status in terms of "any immunizations" versus "no immunizations" and obtained an estimate of 0.7. We did not include the estimate of RR for poliomyelitis immunization because one of the cells in the related fourfold table contained a zero value. All 33 cases and 96 of 98 controls had received this immunization (RR = 0). In general, the RR deviated most from unity for those immunizations that might have a greater discretionary component on the part of the family (i.e., immunizations given latest in infancy).

*Past medical history.*—We found an RR of 4.1 (exact

TABLE 3.—*Childhood RMS risk factors: Family medical history*

| Family history of | No. of cases (%) | No. of controls (%) | RR | 95% confidence interval |
|---|---|---|---|---|
| "Hereditary diseases" | 17 (53) | 53 (54) | 1.0 | 0.4–2.2 |
| Congenital birth defects | 14 (42) | 34 (34) | 1.4 | 0.6–3.2 |
| Cancer (all relatives) | 26 (79) | 61 (62) | 2.3 | 0.9–5.8 |
| Cancer (in parents or siblings only) | 2 (6) | 8 (8) | 0.7 | 0.1–3.6 |
| Heart disease | 30 (91) | 87 (88) | 1.4 | 0.4–5.2 |
| Frequent and/or serious infections | 14 (42) | 28 (28) | 1.9 | 0.8–4.2 |
| Asthma or allergies (all relatives) | 23 (70) | 47 (47) | 2.5 | 1.1–5.8 |
| Asthma or allergies (in parents or siblings only) | 12 (36) | 21 (21) | 2.1 | 0.9–5.0 |
| Any relative receiving "allergy shots" | 3 (9) | 20 (21) | 0.4 | 0.1–1.3 |
| Psychiatric and/or neurologic disease | 14 (42) | 34 (35) | 1.4 | 0.6–3.1 |
| Anemia | 7 (21) | 11 (11) | 2.1 | 0.8–6.0 |
| Death of subject's sibling | 4 (12) | 8 (8) | 1.5 | 0.4–5.3 |

TABLE 4.—*Childhood RMS risk factors: Gestational and parturitional histories*

| Risk factors | No. of cases (%) | No. of controls (%) | RR | 95% confidence interval |
|---|---|---|---|---|
| Mother's prior miscarriage | 5 (19) | 10 (11) | 1.9 | 0.6–6.2 |
| Mother's illness during pregnancy with subject | 24 (73) | 70 (74) | 1.0 | 0.4–2.3 |
| Mother's cigarette smoking during pregnancy | 9 (28) | 27 (28) | 1.0 | 0.4–2.4 |
| Mother's consumption of alcohol during pregnancy | 4 (13) | 16 (17) | 0.7 | 0.2–2.4 |
| Radiographic examination during pregnancy | 2 (6) | 11 (12) | 0.5 | 0.1–2.4 |
| Weight gain during pregnancy (>11.3 vs. ≤11.3 kg) | 10 (34) | 32 (36) | 0.9 | 0.4–2.2 |
| Medications used by mother during and/or 1 yr prior to pregnancy: | | | | |
| Aspirin | 3 (72) | 64 (70) | 1.1 | 0.5–2.7 |
| Antibiotics | 13 (43) | 19 (22) | 2.7 | 1.1–6.5 |
| Pain or cold remedies | 10 (34) | 28 (32) | 1.1 | 0.5–2.7 |
| Tranquilizers | 2 (7) | 5 (5) | 1.3 | 0.2–6.9 |
| Oral contraceptives or other birth control methods | 8 (25) | 23 (24) | 1.0 | 0.4–2.6 |
| Drugs for menstrual disorders or infertility | 2 (6) | 5 (5) | 1.2 | 0.2–6.4 |
| Length of pregnancy: | | | | |
| Premature delivery (vs. normal) | 4 (18) | 19 (24) | 0.7 | 0.2–1.8 |
| Overdue delivery (vs. normal) | 10 (36) | 13 (18) | 2.6 | 1.1–7.1 |
| Length of labor (>10 hr vs. ≤10 hr) | 10 (36) | 25 (27) | 1.5 | 0.6–3.7 |
| Mother's age at subject's birth (>30 vs. ≤30 yr) | 9 (27) | 12 (13) | 2.6 | 1.0–6.8 |
| Type of delivery (forceps or cesarean vs. other) | 8 (24) | 11 (12) | 2.4 | 0.9–6.6 |
| Place of delivery (hospital vs. home) | 31 (94) | 93 (94) | 1.0 | 0.2–5.2 |

TABLE 5.—*Childhood RMS risk factors: Neonatal history*

| Risk factors | No. of cases (%) | No. of controls (%) | RR | 95% confidence interval |
|---|---|---|---|---|
| Birth weight (>3.4 vs. ≤3.4 kg) | 14 (44) | 40 (42) | 0.9 | 0.5–2.4 |
| Birth length (>50 vs. ≤50 cm) | 7 (35) | 21 (48) | 0.6 | 0.2–1.8 |
| Congenital malformations | 8 (24) | 18 (19) | 1.4 | 0.5–3.5 |
| Circumcision (males) | 19 (83) | 58 (89) | 0.6 | 0.2–2.2 |
| Conditions requiring medical treatment | 2 (6) | 12 (13) | 0.4 | 0.1–2.0 |
| Newborn infections | 1 (3) | 4 (4) | 0.7 | 0.1–6.5 |
| Jaundice | 1 (3) | 8 (8) | 0.3 | 0.04–2.6 |
| Diarrhea and/or unusual vomiting | 2 (6) | 8 (9) | 0.7 | 0.1–3.4 |
| Feeding problems | 1 (3) | 5 (5) | 0.6 | 0.1–4.8 |

$P=0.05$) associated with prior history of whooping cough and of 4.3 for impetigo (exact $P=0.07$) (table 8). There was also an increased history of measles (RR = 2.0) and of asthma (RR = 2.5) in cases. However, there was no association between RMS and history of infectious diseases for which no immunizations are available, such as otitis media or chickenpox (RR = 0.9 for both). The RR associated with scarlet fever was 0.5.

*Miscellaneous factors.*—Table 9 summarizes our evaluation of a number of miscellaneous potential risk factors. Fathers who were ever-smokers (relative to those who were never-smokers) conferred an RR of 3.9 ($P=0.003$). This finding was in contrast to the findings of an RR of 0.8 for children of mothers who were ever-smokers and of 1.0 for children of mothers who smoked cigarettes during their pregnancy.

TABLE 6.—*Childhood RMS risk factors: Childhood environment*

| Risk factors | No. of cases (%) | No. of controls (%) | RR | 95% confidence interval |
|---|---|---|---|---|
| No. of people dwelling in home (>5 vs. ≤5) | 4 (12) | 15 (15) | 0.8 | 0.2–2.5 |
| No. of rooms in homes (≤5 vs. >5) | 21 (64) | 53 (55) | 1.5 | 0.6–3.3 |
| Sharing of bedroom by subject | 25 (78) | 74 (75) | 1.2 | 0.5–3.1 |
| Any pet animals | 27 (82) | 85 (86) | 1.7 | 0.3–2.1 |
| Dogs | 24 (75) | 75 (77) | 0.9 | 0.3–2.2 |
| Cats | 16 (50) | 41 (42) | 1.4 | 0.6–3.0 |
| Indoor plumbing | 27 (82) | 74 (76) | 1.5 | 0.5–4.0 |
| Water source (city or town water vs. other) | 13 (39) | 36 (36) | 1.1 | 0.5–2.6 |
| Pesticide exposure | 3 (9) | 6 (6) | 1.5 | 0.4–6.5 |
| Rodenticide exposure | 1 (3) | 3 (3) | 1.0 | 0.1–9.9 |
| Other chemical exposures | 7 (22) | 8 (8) | 3.2 | 1.1–9.2 |
| Any exposure to pollution from factories or plants | 6 (19) | 11 (11) | 1.9 | 0.6–5.6 |
| Exposure to chemicals from factories | 2 (6) | 2 (2) | 3.3 | 0.5–22 |
| Exposure to fumes from factories | 3 (10) | 9 (9) | 1.0 | 0.3–4.2 |
| Exposure to dust from factories | 1 (3) | 3 (3) | 1.0 | 0.1–10.5 |
| Exposure to waste from factories | 2 (6) | 5 (5) | 1.2 | 0.2–6.8 |
| Subject's travel abroad | 2 (6) | 5 (5) | 1.2 | 0.2–6.6 |
| Exposure to playmate who had cancer | 1 (3) | 2 (2) | 1.5 | 0.1–17 |

TABLE 7.—*Childhood RMS risk factors: Diet*

| Risk factors | No. of cases (%) | No. of controls (%) | RR | 95% confidence interval |
|---|---|---|---|---|
| Subject's egg consumption (>4 vs. ≤4/wk) | 12 (41) | 35 (36) | 1.3 | 0.5–2.9 |
| Use of butter vs. margarine | 2 (6) | 6 (6) | 1.0 | 0.2–5.4 |
| Family's use of animal fat vs. vegetable oil in cooking | 2 (6) | 13 (15) | 0.4 | 0.1–2.0 |
| Formula vs. breast feeding in infancy | 23 (72) | 61 (63) | 1.5 | 0.6–3.6 |
| Daily milk consumption (>0.95 vs. ≤0.95 liter) | 5 (17) | 19 (20) | 0.8 | 0.3–2.3 |
| Use of whole vs. other milk | 22 (73) | 71 (75) | 0.9 | 0.4–2.4 |
| Luncheon meat consumption (>4 vs. ≤4 times/mo) | 17 (55) | 47 (50) | 0.8 | 0.4–1.9 |
| Hotdog consumption (>4 (vs. ≤4 times/mo) | 11 (34) | 29 (31) | 1.2 | 0.5–2.8 |
| Ham consumption (>4 vs. ≤4 times/mo) | 3 (10) | 8 (9) | 1.1 | 0.3–4.5 |
| Bacon consumption (>4 vs. ≤4 times/mo) | 20 (63) | 48 (52) | 1.5 | 0.7–3.5 |
| Sausage consumption (>4 vs. ≤4 times/mo) | 13 (41) | 37 (40) | 1.0 | 0.4–2.3 |
| Organ meat consumption | 21 (70) | 37 (39) | 3.7 | 1.5–8.3 |
| Frequency of family's purchase of 1 pound of salt (once/mo or more vs. other) | 11 (35) | 33 (34) | 1.1 | 0.4–2.5 |
| Subject's use of salt at table (yes vs. no) | 19 (59) | 48 (52) | 1.4 | 0.6–3.1 |
| Subject's use of food substitutes | 5 (16) | 18 (18) | 0.8 | 0.3–2.4 |
| Family's use of diet foods or beverages | 2 (6) | 6 (6) | 1.0 | 0.2–5.2 |
| Family's use of saccharin | 7 (22) | 15 (16) | 1.5 | 0.6–4.1 |
| Family consumption of meats: | | | | |
| Beef (>2 vs. ≤2 times/wk) | 16 (50) | 53 (54) | 0.9 | 0.4–1.9 |
| Pork (>2 vs. ≤2 times/wk) | 9 (28) | 19 (20) | 1.6 | 0.6–4.0 |
| Chicken (>2 vs. ≤2 times/wk) | 7 (22) | 17 (17) | 1.4 | 0.5–3.6 |
| Fish (>2 vs. ≤2 times/wk) | 4 (13) | 16 (16) | 0.7 | 0.2–2.4 |

*Assessment of confounding by SES.*—Because we were concerned that some of our findings might be confounded by SES, we controlled for family income and fathers' education and occupation in a matched logistic regression analysis of fathers' cigarette smoking and of smallpox vaccination status. In the analysis of fathers' smoking, we obtained an adjusted RR of 2.8 ($P=0.07$). In the analysis of smallpox vaccination, we obtained an adjusted RR of 0.2 ($P=0.009$). Due to incomplete data, the number of subjects included in these analyses was smaller than that in the univariate analyses.

TABLE 8.—*Childhood RMS risk factors: Subject's medical history*

| Risk factors | No. of cases (%) | No. of controls (%) | RR | 95% confidence interval |
|---|---|---|---|---|
| Smallpox vaccination | 21 (66) | 88 (90) | 0.2 | 0.1–0.6 |
| Measles-mumps-rubella immunization | 29 (91) | 93 (97) | 0.3 | 0.1–1.5 |
| Diphtheria-tetanus-pertussis immunization | 32 (97) | 96 (98) | 0.7 | 0.1–7.6 |
| Overall immunization status (ever vs. never) | 32 (97) | 96 (98) | 0.7 | 0.1–7.6 |
| Measles | 14 (42) | 25 (27) | 2.0 | 0.9–4.6 |
| Mumps | 13 (39) | 33 (34) | 1.3 | 0.6–2.9 |
| Rubella | 5 (16) | 21 (23) | 0.6 | 0.2–1.8 |
| Pertussis | 5 (15) | 4 (4) | 4.1 | 1.1–15 |
| Chickenpox | 23 (70) | 70 (73) | 0.9 | 0.4–2.0 |
| Scarlet fever | 1 (3) | 6 (6) | 0.5 | 0.1–3.9 |
| Hepatitis | 1 (3) | 5 (5) | 0.6 | 0.1–5.0 |
| Pneumonia | 2 (6) | 8 (8) | 0.7 | 0.2–3.6 |
| "Strep throat" | 10 (30) | 28 (29) | 1.1 | 0.4–2.5 |
| Otitis media | 10 (30) | 31 (32) | 0.9 | 0.4–2.2 |
| Impetigo | 4 (12) | 3 (3) | 4.3 | 1.0–18 |
| Warts | 5 (16) | 12 (14) | 1.2 | 0.4–3.6 |
| Asthma | 3 (9) | 4 (4) | 2.3 | 0.5–11 |

## DISCUSSION

This study uncovered a number of potential risk factors for RMS. First, we found a confluence of associations with variables related to SES. We found that both mothers and fathers of cases had received less education than control parents, that case parents' occupations tended to be of a lower income and prestige level, and that total family income for cases was lower than that for controls. Whereas only mothers'

TABLE 9.—*Childhood RMS risk factors: Miscellaneous factors*

| Risk factors* | No. of cases (%) | No. of controls (%) | RR | 95% confidence interval |
|---|---|---|---|---|
| Fathers who smoke cigarettes (ever) | 23 (77) | 40 (46) | 3.9 | 1.5–9.6 |
| Mothers who smoke cigarettes (ever) | 8 (26) | 29 (31) | 0.8 | 0.3–2.0 |
| Religion (Protestant vs. other) | 26 (81) | 68 (81) | 1.0 | 0.4–2.9 |
| Birth order (first vs. other) | 13 (39) | 41 (41) | 0.9 | 0.4–2.1 |
| No. of children in sibship (>5 vs. ≤5) | 7 (21) | 14 (14) | 1.6 | 0.6–4.5 |
| Father's age at subject's birth (>30 vs. ≤30 yr) | 7 (22) | 25 (26) | 0.8 | 0.3–2.0 |
| Marital status of mother (married vs. other) | 23 (70) | 73 (75) | 0.8 | 0.3–1.8 |
| Current residence (in town of ≥5,000 vs. <5,000) | 20 (61) | 61 (63) | 0.9 | 0.4–2.0 |
| Farm residence (ever vs. never) | 2 (6) | 6 (6) | 1.0 | 0.2–5.2 |
| Current residence (outside an SMSA vs. in an SMSA) | 23 (70) | 62 (64) | 1.3 | 0.6–3.0 |

* SMSA = standard metropolitan statistical area.

educational level showed a statistically significant association with RMS and family income was at the margin of statistical significance, all of these factors, in the aggregate, suggested that low SES is a risk marker for RMS. Our characterization of lost and nonparticipating controls and comparisons with participating controls suggested that if our selection and location procedures introduced any SES bias, it was of a conservative nature.

Other studies that examined childhood cancer risk in relation to social class have dealt primarily with leukemia. Stewart et al. (*9*) found no association between social class (as indexed by father's occupation alone) and the risk of leukemia or of all childhood cancers. Fasal and co-workers (*10*), using birth and death certificates of children who died of leukemia, found a small but statistically significant increase in leukemia risk for children of high social class (RR = 1.33; $\chi_1^2$ = 4.58), with social class defined by fathers' occupation. Although prior studies have found no or weak associations between social class and childhood cancer risk, these studies have been limited by having minimal data available for the classification of families' social class.

Perhaps our most salient finding is the strong association between RMS and fathers' cigarette smoking. This finding has two possible explanations. First, a direct carcinogenic effect may be introduced either in a prezygotic manner or by passive inhalation of cigarette smoke by the patients. In support of a direct effect are two studies suggesting a mutagenic effect of fathers' cigarette smoking. Evans and co-workers (*11*) found morphologic sperm abnormalities in cigarette smokers, and Mau and Netter (*12*) showed a twofold increase in the occurrence of severe malformations in children of fathers who were heavy cigarette smokers. The second interpretation relates to SES. Wynder and Hoffmann (*13*) showed that cigarette smoking is inversely related to educational level among men but not among women. Thus the positive finding for fathers but not for mothers may relate to our observation that low SES may be a marker of increased RMS risk. However, the results of our matched logistic regression analysis suggest that this is not a likely explanation. We believe the first hypothesis deserves further consideration.

Most of the numerous studies of mothers' cigarette smoking and risk of malformation in their offspring have shown no or weakly positive associations. The U.S. Surgeon General's 1979 Report on Smoking and Health (*14*) concluded: "There is no convincing evidence that maternal smoking increases the incidence of congenital malformations. Results of published studies, reviewed in the 1973 report (*15*), show relative risks for smokers versus nonsmokers ranging from 0.51 to 1.55." Thus if Mau and Netter's findings (*12*) prove valid, our observation of a possible association between fathers' (but not mothers') cigarette smoking and risk of RMS appears even more worthy of further study.

Several studies have directly examined cancer risk of children in relation to their parents' smoking status (*9, 16–18*). All have shown little or no association between mothers' smoking and cancer risk in their offspring and therefore are consistent with our findings. We found only one study that evaluated the association between fathers' smoking and risk of cancer among their children. Stewart et al. (*9*) found that fathers of children with leukemia were only slightly more apt to be smokers than those of control children, but the authors point out that their analysis was crude.

We found internal consistency in our study when we examined immunization status and history of infectious diseases. Cases had received remarkably fewer immunizations than had controls and, conversely, they had contracted more of those diseases preventable by immunization. The association of RMS with impetigo, a disease associated with poor hygiene, was also interesting. Our finding of an association with history of pertussis is similar to an observation made by Bross and Natarajan (*19*) in a study of children with leukemia. These investigators found a twofold increase in leukemia risk for children with a history of antecedent bacterial infection (defined as "pneumonia, whooping cough, or dysentery").

Our findings of fewer immunizations in cases are similar to those in Neumann's study (*20*) of children dying of cancer in Baden-Württemberg, Federal Republic of Germany. Neumann found statistically significantly less diphtheria immunization in case children than matched controls (RR = 0.25). His cases had less tetanus (RR = 0.46), poliomyelitis (RR = 0.75), and BCG (RR = 0.69) immunizations but more smallpox vaccination (RR = 1.28) than did his controls, though these differences were not statistically significant. All of his findings are consistent with ours except for those with regard to smallpox vaccination. This would suggest that the specific immunizations are not themselves risk factors, but that immunization status per se is a risk marker for childhood cases.

We found a notable association with exposure to chemicals and chemical pollution. Cases also appeared to have eaten more organ meats than did controls and somewhat more pork (RR = 1.6). The increased consumption of organ meat and pork may be interrelated in that NC farmers (and rural families) who slaughter their own pigs will usually utilize all organ and "variety" meats.

We found associations between RMS and several gestational and parturitional factors. These include a positive association with an overdue delivery and, conversely, a negative association with premature delivery of the propositus. Additionally, use of forceps and cesarean section in the delivery of subjects and use of antibiotics by mothers during the year and 9 months preceding the birth of their children appear to be risk markers of RMS. We found an interesting association with mothers' age at birth of subjects. Similar observations were made in earlier studies, which showed that mothers of children with leukemia were significantly older than mothers of controls (*9, 16, 21*). One of these

studies (*9*) showed that the increased risk of leukemia with increasing maternal age was independent of the occurrence of Down's syndrome. Another study showed a "consistent, although not statistically significant, trend toward increasing rates with increasing maternal age" for all childhood cancers (*21*).

The findings of an association with history of asthma and allergies in families and of an RR of 2.3 for history of asthma in subjects suggest that immunologic factors play a role in the etiology of RMS. Bross and Natarajan (*19*), in their case-control study of childhood leukemia, similarly found a three-fold increase in risk associated with subjects' history of antecedent allergic diseases (asthma and hives). Manning and Carroll (*16*) showed similar results more than 20 years ago. They also found a statistically significant association between risk of childhood leukemia (and lymphoma) and mothers' history of having had allergic diseases. However, there was no increased history of allergies for children with other cancers or their mothers.

In summary, we have found a number of potential risk factors for childhood RMS. We found immunization status, fathers' cigarette smoking, diet, chemical exposures, mothers' age, gestational factors, asthma, and SES to be associated with RMS. In particular, we believe that the association with fathers' smoking is deserving of further evaluation. The aggregate of our findings implies that environmental factors may play an important role in the etiology of childhood RMS. We must, however, caution that this is the first case-control study of this rare cancer and that our study size was small. Further investigation is needed to confirm our findings in another setting.

We believe that the issue of environmental factors in the etiology of childhood cancers has not been explored adequately. The relatively short latent periods between potential etiologic exposures and disease manifestation in children provide unique opportunities for the study of environmental factors. Similar case-control studies of other childhood cancers might provide important new etiologic leads.

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